Medicinal Herbs can Play Significant Role in Attenuation of Ischemia and Reperfusion Injury

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Withania somnifera (Ws), Curcuma longa *Ocimum sanctum (Os)*, and herbal combination (HCB) including {*Ws* *Cl* *Os* (75 mg/kg} to limit injury in the setting of myocardial ischemia and reperfusion was explored in the present study.

experimental model. Wistar albino rats were divided into ten groups and orally fed saline once daily (sham, control IR) or medicinal herbs (Ws/Cl/Os/HCB; Ws-IR, Cl-IR/Os-IR/HCB-IR) respectively for 1 month. On the 31

day in the rats of the Control IR and Ws-IR, Cl-IR/Os-IR/HCB-IR groups, LAD was occluded for 45 min, and reperfused fo˜ and ! } points and subsequently sacriýced for biochemical, immunohistochemical and pathological studies. In the control IR group, signiýcant ventricular dysfunction, cardiac necrosis, apoptosis; decline in antioxidant status and elevation in lipid peroxidation was observed. Chronic oral a gr þ a ! Ŧ

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In the present study 25, 50 &100 mg/kg doses of Ws; 25, 50, 100 & 200 mg/kg doses of Cl and 25, 75 & 150 mg/kg of Os were screened in the ISP model of myocardial necrosis in rats. Ws (50 mg/kg), Cl (100 mg/kg) and Os (75 mg/kg) were found to be most e ective for functional recovery of the myocardium and the favorable restoration of biochemical and histopathological alterations. Hence, these doses were selected for further evaluation in the ischemia and reperfusion model of myocardial injury in rats.

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Post-ischemic reperfusion injury resulted in signi cant cardiac necrosis, apoptosis; depression of le ventricular dynamics, peripheral hemodynamics (mean blood pressure) and heart rate; and decline in antioxidant status and elevation in lipid peroxidation. In addition, consistent with the increase in TUNEL staining in the control IR group, ischemia and reperfusion slightly reduced Bcl-2 expression and signi cantly increased Bax expression ($p<0.01$) compared with that observed in the sham group, demonstrating the phenomenon of ischemia and reperfusion induced enhanced myocardial apoptotic cell death.

***Withania Somnifera*:** Augmentation of myocardial endogenous antioxidant reserve {SOD, CAT, GSHPx ($p<0.01$)} following chronic oral administration of Ws to healthy controls (study group of animals without any experimental challenge to the myocardium; via ISP administration or inducing ischemia and reperfusion injury) signi cantly improved defense against oxidative stress as compared to the sham group (oral administration of saline for one month to healthy experimental animals). Further, Ws treatment favorably reestablished the ischemia-reperfusion-induced abnormality of le ventricular functions {(+)LVdP/dt, (-)LVdP/dt and LVEDP}, restored the myocardial oxidant-antioxidant 9 (n)2l oar dh,2 (m)1venmt12 (nic)]T6626s (t)-5 (o)]T0e mohf sahioent0312 (ra)8trtBBch4euced enion of3 (es) the mm gr4stanh56 (a)-4.8(e)(uce)-bxidrd19 (t)(e f)9 (o)112 (n--5 (og)0.5 (a))3 819o

oxygen demand and supply was done in the present study to assess this critical balance and the functional status of the heart specifically the left ventricular dynamics. Furthermore, the extent of myocardial injury couples with the degree of left ventricular dysfunction. Therefore, hemodynamic monitoring is essential to assess response to therapy. Because no single hemodynamic variable can reliably predict the outcome of myocardial ischemia and the effectiveness of a therapeutic approach, a combination of hemodynamic indices has been used to improve the value of hemodynamic monitoring. Alterations in MAP, HR, LVEDP, (+) LVdP/dt and negative (-) LVdP/dt during coronary artery ligation and reperfusion have been studied in different experimental groups.

In the present study, on occlusion of the LAD coronary artery there was a significant fall in MAP in conjunction with a non- significant change in HR. However fall in both these parameters progressed with the duration of ischemia and reached statistical significance at 45 min of ischemia. Coronary artery occlusion for 45 min and subsequent reperfusion for 60 min, resulted in a marked depression in myocardial contractility and diastolic function as evidenced by a fall in (+) and (-) LVdP/dt in concert with a significant elevation of LVEDP. Similar observations have been reported by other workers [6].

Following reperfusion, a further fall in MAP and HR was observed, which was sustained till the end of the reperfusion period. Fall in MAP ideally elicits reflex sympathetic activation, which should have increased HR. However, the significant fall in HR observed in the present study may be due to:

i) Anesthesia induced blunting of the reflex neural activity

ii) Fall in MAP might not be biologically adequate for a reflex neural activation

iii) Impairment of conduction (A-V block) of the heart following ischemia and reperfusion induced injury

Reperfusion of the ischemic myocardium also caused a further significant decrease in both (+) and (-) LVdP/dt, which failed to recover over the entire period of reperfusion. Such deterioration in the hemodynamic functions during reperfusion as observed in the present study is suggestive of an injury occurring following reinstitution of blood flow into the regionally ischemic myocardium. Similar observations (popularly known as ischemia and reperfusion injury) have also been made by several investigators in different experimental models [7]. Hasan and McDonough [6], have reported that reperfusion of the ischemic myocardium resulted in a significant and prolonged depression of contractile function in a rat model. Depression of (+) LVdP/dt has also been reported in a rat model subjected to ischemia and reperfusion. Reperfusion of the ischemic myocardium was effective in lowering LVED.d-8 (v) [illegible]

vascular remodeling processes. Induction of apoptosis is implicated in cardiac dysfunction. Not only ROS *per se*, but also their oxidative products and their secondary messenger molecules generated by ROS can trigger the programmed cell death. TUNEL positivity and the immunohistochemical localization of Bax, an inducer of apoptosis and Bcl-2 proteins, inhibitors of apoptosis were studied to delineate the involvement of apoptosis in ischemia and reperfusion induced injury.

e TUNEL assay identi es single strand DNA breaks with free 3'-OH terminals. Seen-2d-,i4 (en-2)10 (udie)-5 (ds h-4.9 (18(e)]TJ0n)4 (d)-8 (c)6 (hd in)19 50.113 d(N)38 ((l)2-,i41 (d t)-82-,i1 (t)6 (os(l)3 (s))]TJ0.068 Tw

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TUNEL positive cells in the ischemic myocardium, Ws treatment upregulated the expression of anti-apoptotic protein, Bcl-2 and down regulated the expression of pro-apoptotic protein, Bax. ese e ects may signi cantly reduce the marked apoptotic cell death in the myocardium of the control IR group. e anti-apoptotic property of Ws has been reported earlier in a rat model of stroke [30].

On the basis of the obtained hemodynamic, biochemical and histopathological data, it was concluded that Ws is a highly e ective cardioprotective agent. e favorable modulation of ventricular function, signi cant antioxidant and anti-apoptotic properties may contribute to the bene cial e ects of Ws [31]. e study provides scienti c rationale for the use of Ws in Ayurveda, the ancient Indian system of medicine known as Maharasayana [24].

Curcuma longa

) **D e e ec d e *Curcuma longa*:** e cardioprotective e ects of 25, 50, 100 and 200 mg/kg *Curcuma longa* (Cl), a perennial herb used in Ayurveda, the Indian System of Medicine, as a general health tonic and healing agent, were studied in the ISP model of MI. Cl (Turmeric), common Indian dietary pigment and spice has been shown to possess a wide range of therapeutic utilities in the traditional Indian medicine. It's role in wound healing, urinary tract infections, liver ailments are well-documented [32]. e active component of turmeric identi ed as curcumin exhibits a variety of pharmacological e ects including antioxidant, adaptogenic, anti-in ammatory and anti-infectious activities [33]. However, only few studies are presently available that documents its cardioprotective potential.

and bio-availability enhancers to expedite the transfer of the bene ts of the formulation to the parts of the physiology. e most complex of the traditional Ayurvedic herbal combinations are an elite group called rasayanas, extolled at length in the Ayurvedic texts for their positive impact on the physiology [43].

e second principle, 'sanskar', refers to the way the herbs are harvested, used and processed. Ayurvedic formulations traditionally use the whole herb instead of extracting the active ingredient from the plant. Nature's healing wisdom is perceived to reside best in the plant in its entirety. Using the whole herb rather than the isolated ingredient also contributes to a balanced formula less likely to have side-e ects, because according to Ayurveda, each medicinal plant has both the primary e ect and the antidote present in it in its natural state.

) C a ebe e : e Ayurvedic approach to health is gentle and comprehensive. e concepts of instant cures and pill-popping for immediate relief are foreign to Ayurveda. Because the endeavor is to seek and correct the source of problems -- imbalances in the physiology -- the best results from Ayurveda come to those who are patient and persistent, who diligently adopt the associated dietary and lifestyle changes needed, and take a degree of responsibility for their own well-being. For those who do make this commitment, Ayurveda o ers rich, cumulative health bene ts that can help you enjoy a long, healthy and blissful life [44].

M ca d a c e ce f e e e ba c b a (HCB): *Withania somnifera* (50 /) + *Curcuma longa* (100 /) + *Ocimum sanctum* (75 /) . a d V a Ed c e aa d e e f : e HCB was e ective enough to signi cantly ameliorate myocardial ischemic injury following LAD coronary occlusion and reperfusion when compared to control IR group. A signi cant nding of the present study is that the cardioprotection extended by the herbal combination was superior compared to that extended by the herbal extracts administered alone.

HCB did not signi cantly a ect MAP and HR during the ischemic period; however during the latter half of the reperfusion period, HCB and Lsp, signi cantly restored MAP and HR. However, the modest bene cial hemodynamic e ects on HR and MAP exerted by HCB do not explain the marked cardioprotection observed during ischemic and reperfusion injury. In contrast, Vit E did not exhibit any signi cant e ect on these parameters.

In the present study, HCB exerted bene cial e ects on le ventricular dynamics as evidenced by (a) the correction of the ischemia-reperfusion induced enhanced level of LVEDP and (b) by signi cant improvement in myocardial contractility and relaxation. It appears that the herbal extracts are more e ective when administered together in preventing the hemodynamic deteriorations observed in the control IR group. However, Lsp treatment demonstrated superior recovery in le ventricular function as compared to HCB and Vit E. In the Vit E treated group, measurement of le ventricular diastolic function and systolic function revealed correction of LVEDP and partial prevention of the diastolic dysfunction; that is an increased (-) LVdP/dt. However, a parallel protective e ect on the contractile status of the heart (+) LVdP/dt was not observed.

It is well known that one of the major causes of myocardial infarction is an imbalance between oxidants and antioxidant defenses. Hence, it is possible to prevent or ameliorate disease progression by favoring the balance towards lower oxidative stress. Potential antioxidant therapy should, therefore, include exogenous supplementation of natural antioxidants that a ect augmentation of endogenous antioxidants [45].

In the present study, chronic treatment with HCB augmented basal endogenous antioxidants and inhibited the increase in TBARS levels i.e enhanced the antioxidant reserve, favorably modulating the antioxidant defense mechanisms of the myocardium in the healthy experimental animals. However, chronic treatment (30 days) with Lsp and Vit E *per se* did not show any marked e ect on the baseline oxidant-antioxidant parameters. However, a key question, which remains unanswered in the present study, is the mechanism by which HCB augments basal endogenous antioxidants. Although the precise mechanisms of such an e ect are not clear from the present protocol, several factors might be playing contributing roles. In this regard it has been reported earlier that both Ws and Os possess adaptogenic properties; hence, it is speculated that they may contribute to the myocardial adaptogenic activity observed in the HCB control group. Subsequent to ischemia and reperfusion induced oxidative stress it was observed that the HCB, Lsp and Vit E group demonstrated signi cant antioxidant property, which might contribute to the observed cardioprotective e ect of these interventions.

In addition, in the present study, HCB and Lsp demonstrated signi cant anti-apoptotic potential as it upregulated the expression of anti-apoptotic proteitude

administration of the combination of the herbs under investigation

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